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EXAMINER	
MOORE, SUSANNA	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/083,245	DARROW ET AL.	
	Examiner	Art Unit	
	SUSANNA MOORE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-12,18-41,45,46 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-12,18-41,45,46 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

The request for reconsideration of petition under 37 C.F.R. 1.1819(a) to withdraw the holding of abandonment has been granted. Thus, reconsideration by the Examiner of the finality of the last Office action has caused the finality to be withdrawn, and thus, prosecution is reopened. This is a Nonfinal Office Action since new rejections are being applied. In summary, claims 1, 7-12, 18-41, 45, 46 and 51 are currently pending.

Specification

Applicant has submitted an amendment to the PGPublication. However, if Applicant would like to amend the Specification, Applicant should submit the amendments based on the disclosure, not the PGPub. Thus, note the amendment, by page, line number, etc.

The abstract of the disclosure is objected to because the phrase "such disorders and well as packaged" should be addressed. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: the term "trifluromethylsulfonyl" is misspelled in several places in the Specification, including page 6, the third line from the bottom of the page, page 7, line 18, page 8, lines 4 and 12. There may be others as well. Appropriate correction is required.

The definition of R^5 on page 8, third full paragraph, repeats "3- or 4- tetrahydropyranyl." Appropriate action is required.

The definition of R^5 on page 7, lines 12-13, define "pyrazolyl" and "1-, 3- or 4-pyrazolyl" as substituents for R^5. Which one does Applicant intend? Appropriate action is required.

Claim Objections

Note: The applicants' are reminded of the manner of making amendments.

37 CFR § 1.121 Manner of making amendments in application.

> (c) Claims. Amendment to a claim must be made by rewriting the entire claim with all changes (e.g., additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an exiting claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims in the amendment document will serve to replace all prior versions of the claims in the application, In the claim listing, the **status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).**

The following claim(s) fail to properly identify the status of the claims. Please check the history of the claims and label accordingly.

Claims 1, 23 and 24 are objected to because of the following informalities: replace "1,2, or 3" with "1, 2 or 3" in claim 1, lines 9 and 15; claim 23, line 9 and 14; and claim 24, line 19. Appropriate correction is required.

Claim 1, 9, 10, are objected to because of the following informalities: the term "trifluromethylsulfonyl" is misspelled in several places in the claims, including claim 1, line 28, 42, 112; claim 9, line 9; claim 10, line 8; claim 23, line 26, 61, 69; claim 24, lines 30, 48 . Appropriate correction is required.

Claims 1, 23 is objected to because of the following informalities: replace "take" with "taken" in claim 1, line 44; claim 23, line 47. Appropriate correction is required.

Claims 18-20 are objected to because of the following informalities: the acronym "NPY" should be defined in said claims. The "NPY" can be placed in parenthesis after the spelled-out word(s). Appropriate correction is required.

Claims 18-20 are objected to because of the following informalities: please remove the phrase "any one of" from claim 18. Appropriate correction is required.

Claim 18 is objected to because of the following informalities: please replace "I" with "1." Appropriate correction is required.

Claim 23 is objected to because of the following informalities: please replace "N $R^{11}SO_2R^7$" with "$NR^{11}SO_2R^7$" in line 35. Appropriate correction is required.

Claim 23 is objected to because of the following informalities: please replace "pyrimimidinyl" with "pyrimidnyl" in line 38. Appropriate correction is required.

Claim 24 is objected to because of the following informalities: please replace "the two and the 2" with "the two" in line 10. Appropriate correction is required.

Claim 24 is objected to because of the following informalities: please replace "C_1-$C_{10,}$" with "C_1-C_{10}" in line 37. Appropriate correction is required.

Claim 26 is objected to because of the following informalities: please remove one of the periods at the end of the claim. Appropriate correction is required.

Claims 27-30 and 32-34 are objected to because of the following informalities: please remove one of the periods at the end of the claim. Appropriate correction is required.

Claim 30 is objected to because of the following informalities: please replace "C_1-C_7, alkyl" with "C_1-C_7 alkyl." Appropriate correction is required.

Claim 32 is objected to because of the following informalities: please replace "tetrahydrofluranyl" with "tetrahydrofuranyl" and replace "cyclhexenyl" with "cyclohexenyl." Appropriate correction is required.

Claim 36 is objected to because of the following informalities: please replace "2-tetrahydonaphthylenyl" with "tetrahydronaphthylenyl." Appropriate correction is required.

Claim 35 is objected to because of the following informalities: please replace "2-pyr,zinyl" with "2-pyrazinyl." Appropriate correction is required.

Claim 1, 23 and 24 are objected to because of the following informalities: please replace "Aryl" with "aryl." Appropriate correction is required.

Claim 1, 23 and 24 are objected to because of the following informalities: please replace "carbons atoms" with "carbon atom" in the definition of B. Appropriate correction is required.

Claims 38-41 are objected to because of the following informalities: there are many typographical errors in claims 38-41. Moreover, there are species listed that are drawn to non-elected subject matter. Appropriate correction is required.

Claims 46 and 51 are substantial duplicates of claim 45 as the only difference is a statement of intended use, which is not given material weight. Note *In re Tuominen 213 USPQ 89*. Claims 45, 46 and 51 are drawn to compositions of compounds of claim 24.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 7-12, 18-41, 45, 46 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Throughout the claims there are many substituents whose valency has been exceeded. For example, the substituent "(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl" should be replaced with "(C_3-C_{10} cycloalkyl) C_1-C_6 alkylene" throughout the claims. Other examples include the following:

"C_1-C_6 alkyl-OR^7" should be replaced with "C_1-C_6 alkylene-OR^7,"

"C_1-C_6 cyanoalkyl" should be replaced with "C_1-C_6 cyanoalkylene,"

"C_1-C_6 alkyl-NR^8NR^9" should be replaced with ""C_1-C_6 alkylene-NR^8NR^9,"

"C_1-C_6 alkyl-$CONR^8NR^9$" should be replaced with ""C_1-C_6 alkylene-$CONR^8NR^9$,"

"C_1-C_6 alkyl-$COOR^7$" should be replaced with "C_1-C_6 alkylene-$COOR^7$,"

"C_1-C_6 alkyl-CN" should be replaced with "C_1-C_6 alkylene-CN,"

"Aryl(C_1-C_6)alkyl" should be replaced with "Aryl(C_1-C_6)alkylene"

"heteroaryl(C_1-C_6)alkyl" should be replaced with "heteroaryl(C_1-C_6)alkylene"

"aryl(C_5-C_8)cycloalkyl" should be replaced with "aryl(C_5-C_8)cycloalkylene"

"heteroaryl(C_5-C_8)cycloalkyl" should be replaced with "heteroaryl(C_5-C_8)cycloalkylene,"

"C_1-C_6 arylalkyl" should be replaced with "C_1-C_6 arylalkylene,"

"C_1-C_6 heteroarylalkyl" should be replaced with "C_1-C_6 heteroarylalkylene,"

"C_1-C_6 alkyl-O C_1-C_6 alkyl" should be replaced with "C_1-C_6 alkyl-O C_1-C_6 alkylene,"

"C_1-C_6 alkyl-OR^3" should be replaced with "C_1-C_6 alkylene-OR^3,"

"C_1-C_6 alkyl-OR^{13}" should be replaced with "C_1-C_6 alkylene-OR^{13},"

The substituents "C_1-C_6 alkenyl" and "C_1-C_6 alkynyl" cannot have only one carbon. See claim 1, line 11, 27, 41, 57, 64; claim 9, line 8; claim 10, line 2; claim 23, lines 25,44, 52, 68; claim 24, lines 29 and 57; claim 33, line 4; claim 35, line 10. Furthermore, claim 24 contains "C_1-C_6 alkynyl" and "C_2-C_4 alkynyl" in lines 29 and 33. Which does Applicant intend?

The definition of R^5, claim 1, lines 107-108; claim 23, lines 39-40; claim 35, lines5-6, define "pyrazolyl" and "1-, 3- or 4-pyrazolyl" as substituents for R^5. Which does Applicant intend?

Claims 8-10 recite the limitation "R^2 is… C_1-C_6 alkyl" but claim 1, from which claims 8-10 depend, does not embrace this subsituent. There is insufficient antecedent basis for this limitation in the claim.

Regarding claims 20, the phrase "100 nanomolar 10 nanomolar" is not clearly defined. Which concentration does Applicant intend? Please correct the claim and so the appropriate concentration is claimed.

In claims 18-20, the term "assay" is not clearly defined. By using the word "assay" an uncertainty exists as to which "assay" Applicant is claiming. The Specification discloses two in vitro assays on pages 101-103 and thus just claiming an assay does not sufficiently define the term "assay."

Claim 23 is drawn to a compound of formula I, but formula I is defined in claim 1, from which this claim does not depend. The Examiner suggests naming the formula in claim 23, formula II.

Claim 24 is drawn to a compound of formula I, but formula I is defined in claim 1, from which this claim does not depend. The Examiner suggests naming the formula in claim 24, formula III.

Claim 24 defines a substituent as "$R^{7(a)}$" but does not further define "$R^{7(a)}$" in the claims. Furthermore, claim 24 defines a substituent as "OR7" and "C_1-C_6 alkyl-OR7" but does not further define these claims.

Claim 26 recites the limitation "R'" but claim 24, from which it depends does not define "R'." There is insufficient antecedent basis for this limitation in the claim.

Claim 28, line 5, states, "(C_3-C_6) C_1-C_2 alkyl" but does not give the substituent for the first carbon count, C_3-C_6.

In claim 51, the term "arthritis" is indefinite. By itself, it is not a standard medical term for a specific disease or groups of related diseases, but a general term denoting inflammation of the joints, and may or may not involve inflammation of other parts of the body such as the nails. It mostly commonly refers to any of osteoarthritis, gouty arthritis, or rheumatoid arthritis. These are three totally different and unrelated disorders, which all have "arthritis" in their name and involve inflammation of the joints.

Claims 1, 7-12, 18-41, 45, 46 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There are many substituents defined in the claims, which are not supported by the Specification. For example, R5 is defined as "heterocycloalkyl" in line 46, which is much broader than the third full paragraph found on page 8, which defines species. The following are more examples:

Claim 23, lines 84, "C_1-C_6 alkyl-OR^3," this substituent is not defined in the Specification

for R^6;

Claim 24, line 9, "cycloalkyl group may be optionally substituted with 1 to 3 R^{7a} groups," the Specification does not provide for this definition on the bottom of page 5;

Claim 24, lines 11, "R^2 may optionally join with R5 and the two and the 2 nitrogen atoms to which they are bound to form a 6 to 10 membered heterocyclic ring optionally substituted at each carbon with $R^{7(a)}$," but the Specification on the top of page 6 does not embrace this definition;

Claim 24 defines R7 without the proviso found in the Specification on page 9, line 11, thus, any substituent in claim 24 which is defined with R7 introduces new matter. For example, "C_1-C_6 alkyl-OR^7" in lines 6, 16, 22, among others and "OR7" in lines 6, 16 and 22, among others throughout claim 24;

Claim 24, line 26, "C_1-C_6 allyl-NR^8NR^9" is not defined in the Specification for R^3;

Claim 24, lines 35-52, C_1-C_6 alkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10}, cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, OR^7, NR^8R^9, (with the proviso that when two OR^7 or NR^8R^9 substiuents are geminally located on the same carbon R^7 is not H and the geminally located OR^7 or NR^8R^9

substitutuents can be taken together to form a C^2- C^4 ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl- NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, oxo, hydroximino, C_1-C_6 alkoximino, $SO_2NR^8R^9$, SO_2R^7, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at…C_7-C_{10} alkyl group" is not defined in the Specification on page 7, lines 5-8;

Claim 24, line 63-64, "C3-C10 cyclalkenyl, or a 3 to 10 membered mono or bicyclic heterocycle" is not supported in the Specification on page 7 or 8;

Claim 26, line 5, defines R3 as being substituted with 1-3 fluorines but the Specification on page 6, lines 7-9 from the bottom of the page, does allow for substitutions;

Claim 27, line 6, the substituent "C_2-C_6 alkyl OH" is not supported in the Specification on pages 6-7;

Claims 28, 31, 34 and 36 define R^8 as "CF_3 or CH_2CF_3" but the Specification on page 9 does provide for such groups;

Claim 30 defines R5 as "C_1-C_7, alkyl" but this group is not disclosed in the Specification on page 7;

Claim 32 defines R^5 as "3- or 4-cyclhexenyl, or 3-cyclopentenyl" however, the

Specification on page 7-8 does not provide for these groups;

Claim 33 defines substituents on R^5 as "CO- C_1-C_4 alkyl" and further substituted by "C1-C3 alkyl,…, OR7,…, COOR7,…, SO2R7, …, aryl, …, heteroary, …, heterocycloalkyl, 3-, 4-, or 5 –(2-oxo-1,3-oxazolidinyl)" but the Specification on pages 7-9 does not provide support for such groups;

Claim 34 defines substituents on R^5 as "acetyl" and further substitutes the aryl and heteroaryl with "OR^7" but the Specification does not embrace these substituents;

Claim 35 defines R^5 as "C_3-C_4 arylcycloalkyl or C_3-C_4 heteroarylcycloalkyl" however, the Specification does not embrace these substituents;

Claim 1, 7-12, 18-41, 45, 46 and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is the Wands factors, which are used to evaluate the enablement question. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); *Ex parte Forman, 230 USPQ 546.* The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the

presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the invention in the instant case, has claims which embrace pyrazolo[1,5-a]pyrimidine compounds. The scope of "prodrug" is not adequately enabled. Applicants provide no guidance as how the compounds are made more active in vivo. The choice of a "prodrug" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrugs will be suitable for the instant invention.

The instant compounds of formula (I) wherein the prodrugs are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by claim 1. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

Claims 1, 7-12, 18-41, 45, 46 and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other forms, does not reasonably provide enablement for hydrates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to hydrates. But the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton*

International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here: there is no evidence that hydrates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that hydrates can be made, or limit the claims accordingly.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(A) Breadth of claims.

(a) Scope of the compounds. The instant claims encompass millions of compounds with a pyrazolopyridine scaffold with a variety of substituents at four different positions.

(b) Scope of the diseases covered. The instant claims are drawn to a method of treating any and all cardiovascular disorders. Cardiovascular disorders embrace a vast array of problems, some of which are contradictory to others. This covers various forms of endocarditis, including verrucous, atypical verrucous (Libman-Sacks) Non-bacterial thrombotic - NBTE (marantic), bacterial, viral, and rickettsial endocarditis. It covers different forms of atresia, including tricuspid atresia without TGV, pulmonic valvular atresia and aortic atresia. It includes assorted cardiomyopathies, including restrictive cardiomyopathy, peripartum cardiomyopathy, hypertrophic cardiomyopathy, and congenital cardiomyopathy. It embraces various forms of aortic Stenosis, including valvular aortic Stenosis, idiopathic hypertrophic sub-aortic stenosis (IHSS), subvalvular aortic stenosis, and supravalvular aortic stenosis. There are all kinds of miscellaneous syndromes, including subclavian steal syndrome, Eisenmenger syndrome, mitral valve prolapse (Barlow) syndrome, Aortic arch syndrome, scimitar syndrome, hypoplastic left heart syndrome, Lutembacher syndrome, and superior vena cava syndrome. It covers various forms of hypertension, including primary (idiopathic) pulmonary hypertension, neonatal pulmonary venous hypertension and pulmonary hypertension. It includes aortic aneurysms, including both thoracic and abdominal, as well as mycotic aneurysm. It covers various types of arrhythmias and atrial fibrillation. It covers elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, and hyperlipoproteinaemias. It covers different forms of

ischaemic heart disease including congestive heart failure and myocardial infarction. It covers a vast array of structural defects such as atrial septal defect (ASD), aorticopulmonary window, egg-on-its-side heart, gooseneck deformity, endocardial cushion defect, arc of Buehler, arc of Riolan, truncus arteriosus, Ebstein's Malformation, azygos continuation of interrupted IVC, Atrioventricular Canal, ventricular septal defect (VSD), abdominal aortic coarctation, aortic pseudo-coarctation, complete endocardial cushion defect, Hypoplastic Left Heart, patent ductus arteriosus (PDA), congenital absence of pulmonary valve, aortic coarctation partial endocardial cushion defect, Single Ventricle, box-like heart, pulmonary sling, Left Ventricle to Right Atrial Shunt, total anomalous pulmonary venous return (TAPVR), partial anomalous pulmonary venous return (PAPVR), and transposition of the great vessels. It covers certain peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis and assorted cerebral vascular diseases including migraine. There is hypotension, which can arise from all sorts of other problems. There are a number of different forms of vasculitis, including Churg-Strauss vasculitis, consecutive vasculitis, granulomatous vasculitis of central nervous system, hypersensitivity vasculitis, (called also allergic or leukocytoclastic vasculitis or leukocytoclastic angiitis which arises from hypersensitivity to an antigenic stimulus), hypocomplementemic vasculitis, isolated vasculitis of central nervous system, nodular vasculitis, overlap vasculitis (polyangiitis overlap syndrome), pulmonary vasculitis including Wegener's granulomatosis, rheumatoid vasculitis, segmented hyalinizing vasculitis (livedo vasculitis), Polyarteritis nodosa, and urticarial vasculitis. There are also specific forms of arteritis, including coronary arteritis, equine viral arteritis, giant cell arteritis (cranial, granulomatous, or temporal arteritis or Horton's disease), infantile arteritis, infectious arteritis, arteritis obliterans (endarteritis obliterans),

rheumatic arteritis, syphilitic arteritis, Takayasu's arteritis (aortic arch, or brachiocephalic arteritis or Martorell's syndrome or pulseless disease), tuberculous arteritis, endarteritis obliterans, arteritis umbilicalis, and verminous mesenteric arteritis. There are different forms of Vascular dementia, including multi-infarct dementia (MID), Binswanger's Disease and Arteriosclerotic Dementia. There is a huge collection of other cardiovascular problems, including thymoma (invasive and non-invasive), admixture lesion, left ventricular hypertrophy, tortuous aorta, aortic laceration pulmonary artery sarcoma, aortic regurgitation, pneumomediastinum (Spontaneous and traumatic), middle mediastinal mass, posterior mediastinal mass, Uhl disease, right ventricular hypertrophy, cardiac rhabdomyoma, acute aortic dissection, pericardial cyst, carotid artery bruit, pulmonary embolism, venous angioma, varicose veins and spider veins, congenital heart disease, pericardial effusion, tetralogy of Fallot, coronary artery calcification, endocardial fibroelastosis, fibromuscular dysplasia (FMD), thromboangiitis obliterans (Buerger disease), left or right ventricular volume overload, situs inversus, neonatal heart failure, myocarditis, arteriosclerosis, atherosclerosis, stroke and many others.

(B) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(C) Direction or Guidance: That provided is very limited. The dosage range information, found on page 20 of the Specification gives 0.1-50 mg/kg per day, which is very broad. Moreover, this is generic, the same for the many disorders covered by the specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for any and all cardiovascular disorders.

(D) State of the Prior Art: These compounds are substituted pyrazolopyridines. So far as the examiner is aware, no substituted pyrazolopyridines of any kind have been used for inhibiting or treating any and all cardiovascular diseases.

(E) Working Examples: The invention is drawn to a method of treating one or more cardiovascular disorders. There are no working examples or even animal models, in the Specificaiton drawn to this utility to support the use of substituted pyrazolopyridines to treat any and all cardiovascular disorders. On pages 101-105 of the Specification there are several in vitro and in vivo assays presented for the NPY receptor but no data is presented.

(F) Skill of those in the art: These diseases and disorders disclosed in the Specification on pages 16-17 can not be treated generally by any one drug. These are all different diseases and disorders, which occur at different locations and by different modes of action in the body.

(G) The quantity of experimentation needed: Owing especially to factors A, C, E and F, the amount of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim 11, 21, 46 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(A) Breadth of claims.

(a) Scope of the compounds. The instant claims encompass millions of compounds with a pyrazolopyridine scaffold with a variety of substituents at four different positions and the millions of compositions of claims 46 and 51.

(b) Scope of the diseases covered. The instant claims are drawn to a method of treating any eating disorder. An eating disorder is a compulsion in which the main problem is a person eats in a way which disturbs their physical health. The eating may be too excessive (compulsive over-eating), too limited (restricting), may include normal eating punctuated with episodes of purging, may include cycles of binging and purging, or may encompass the ingesting of non-foods. The best-known eating disorders are Anorexia nervosa, Bulimia nervosa, and Pica. There are numerous theories as to the causes and mechanisms leading to eating disorders. The two most common eating disorders are anorexia and bulimia. Both of these have severe consequences to a person's health and can even cause death.

Anorexia nervosa is a psychiatric diagnosis that describes an eating disorder characterized by low body weight and body image distortion. Individuals with anorexia often control body weight by voluntary starvation, purging, vomiting, excessive exercise, or other weight control measures, such as diet pills or diuretic drugs.

Bulimia nervosa, more commonly known as bulimia, is an eating disorder. It is a psychological condition in which the subject engages in recurrent binge eating followed by an

intentional purging. This purging is done in order to compensate for the excessive intake of the food and to prevent weight gain.

Pica is an appetite for non-foods (e.g., coal, soil, chalk, etc.) or an abnormal appetite for some things that may be considered foods, such as food ingredients (e.g., flour, raw potato, starch).

Claim 21 is drawn to a method of treating obesity, a condition which is just the opposite of bulimia nervousa. Obesity is a condition in which the natural energy reserve, stored in the fatty tissue of humans and mammals is increased to a point where it is thought to be a significant risk factor in certain health conditions, leading to increased mortality. Obesity is a disease characterized by being overweight. There are many factors that can cause obesity, including genetics, stress, and hypothyroidism just to name a few.

Included in the scope are all the diseases listed in claims 46 and 51, which include, disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dislipidemia, hypertension, memory loss, epileptic seizures, migraine, sleep disorders, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.

A sleep disorder (somnipathy) is a disorder in the sleep patterns of a person or animal. Some sleep disorders can interfere with mental and emotional function. Sleep disorders can be classified into two broad categories:

- Dysomnias - A broad category of sleep disorders characterized by either hypersomnolence or insomnia. The three major subcategories include intrinsic (i.e.,

arising from within the body), extrinsic (secondary to environmental conditions or various pathologic conditions), and disturbances of circadian rhythm. Some dysomnia conditions are, but are not limited to: insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome, periodic limb movement disorder, hypersomnia (including recurrent hypersomnia (Kleine-Levin Syndrome), posttraumatic hypersomnia and "healthy" hypersomnia) and circadian rhythm sleep disorders (including delayed sleep phase syndrome, advanced sleep phase syndrome and non-24-hour sleep-wake syndrome).

- Parasomnias - Any sleep disorder characterized by partial arousals during sleep or during transitions between wakefulness and sleep. Some parasomnia conditions are, but are not limited to: REM sleep behaviour disorder, sleep terror, sleepwalking (or somnambulism), tooth-grinding, bedwetting or sleep enuresis, sudden infant death syndrome (or SIDS) and sleep talking (or somniloquy).

Claim 51 is drawn to a method of treating a sleeping disorder. This includes insomnia, the inability to sleep or remain asleep, while narcolepsy is a condition which is just the opposite of insomnia.

Sexual reproductive disorders can be defined as any disease or disorder affecting the female or male reproductive system. As recited, the scope of the claim can include, but is not limited to, the following:

Females: thyroid disorders, adrenal diseases, liver disease, kidney disease, Kallman syndrome, hypothalamic dysfunction, hyperprolactinemia, hypotuitarism, polycystic ovary

syndrome, anovulation, diminished ovarian reserve, luteal dysfunction, premature menopause, Turner syndrome, ovarian neoplasm, endometriosis, pelvic adhesion, pelvic inflammatory disease, tubal occlusion, uterine malformations, uterine fibroids, Asherman's syndrome, cervical stenosis, antisperm antibodies, insufficient cervical mucus, vaginismus, vaginal obstruction, various intersex conditions, and androgen insensitivity syndrome.

Males: thyroid disorders, Kallman syndrome, hypogonadismthalamic dysfunction, hyperprolactinemia, hypopituitarism, Klinefelter syndrome, seminoma, cryptochidism, varicocele, hydrocele, Vas deferens obstruction, retrograde ejaculation, immunological sterility, hypospadias, impotence, oligospermia, azospermia and asthenozoospermia.

Claim 51 is drawn to a method of treating diseases depending on male or female reproductive systems. The claims do not address any discrimination towards male or female disorders and the disorders encountered between males and females are not the same. Also, all the diseases dependent on the reproductive system found in one gender cannot be treated by any one drug.

Seizures are temporary abnormal electro-physiologic phenomena of the brain, resulting in abnormal synchronization of electrical neuronal activity. They can manifest as an alteration in mental state, tonic or clonic movements, convulsions, and various other psychic symptoms. They are due to temporary abnormal electrical activity of a group of brain cells. The medical syndrome of recurrent, unprovoked seizures is termed epilepsy, but some seizures may occur in people who do not have epilepsy. Seizure is often associated with a sudden and involuntary contraction of a group of muscles. However, a seizure can also be as subtle as marching numbness of a part of body, a brief loss of memory, sparkling or flashes, sensing an unpleasant odor, a strange

epigastric sensation or a sensation of fear. Therefore seizures are typically classified as motor, sensory, autonomic, emotional or cognitive. These include absence, myoclonic, clonic, tonic, tonic-clonic, and atonic seizures.

These are just a few of the diseases covered by said claims.

(B) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(C) Direction or Guidance: That provided is very limited. The dosage range information, found on page 20 of the Specification gives 0.1-50 mg/kg per day, which is very broad. Moreover, this is generic, the same for the many disorders covered by the specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for any and all the disease and disorders embraced by the Scope.

(D) State of the Prior Art: These compounds are substituted pyrazolopyridines. So far as the examiner is aware, no substituted pyrazolopyridines of any kind have been used for inhibiting or treating all the disorders covered by the Scope.

(E) Working Examples: The invention is drawn to a method of treating one or more eating disorders. On pages 101-105 of the Specification there are several in vitro and in vivo assays presented for the NPY receptor but no data is presented drawn to this utility to support the use of substituted pyrazolopyridines to treat any of the disorders encompassed by the Scope.

(F) Skill of those in the art: The eating disorders and obesity disclosed in the Specification on pages 16 can not be treated generally by any one drug. These are all different diseases and disorders, which cannot be treated by any one drug. Bulimia is the opposite of being obese. How can you possibly treat contradictory diseases with one drug? This holds true for narcolepsy and insomnia.

(G) The quantity of experimentation needed: Owing especially to factors A, C, E and F, the amount of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7-12, 21-32, 45, 46 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over He et. al. (U.S. 6124289).

The current invention teaches substituted compounds of the formula in claim 1,

pyrazolo[1,5-a]pyrimidines, and compositions thereof for the many diseases listed in claim 51, where R1= methyl, R3= methyl, R4= substituted phenyl, R2= hydrogen, A= propylene and B= propylene, substituted with an amino group with R5= methyl and R6= hydrogen.

He et. al. teaches compounds of the formula in claim 1, pyrazolo[1,5-a]pyrimidines, where R1= methyl, R3= methyl, R4= 2,4-dichlorophenyl, R2= hydrogen, A= propylene, B= unsubstituted propyl. See column 54, example 18.

He et. al. differs from the instant claims in the substitution of B, an unsubstituted propyl versus Applicants' aminomethyl. The reference teaches that B can be substituted with many substituents, including methylamino according to the genus of formula (1) in column 8 of the reference. See also column 8, lines 50; and column 9, lines 7, 16 and 45-47.

The reference also teaches compounds, where A= alkyl and B= cycloalkyl which may be substituted by hydrogen, alkyl cycloalkyl and cycloalkylalkyl. See column 9, lines 10, 7, 16, and 45-47. Note, there are many compounds which render said claims obvious. These are just a few.

The compositions are found in column 98, lines 7 and the diseases are found in column 1, lines 7-13.

Thus, said claims are rendered obvious by He et. al.

Claims 1, 7-12, 21-32, 45, 46 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilligan et. al. (U.S. 6060478).

The current invention teaches substituted compounds of the formula in claim 1, pyrazolo[1,5-a]pyrimidines, and compositions thereof for the many diseases listed in claim 51, where R1= methyl, R3= methyl, R4= substituted phenyl, R2= hydrogen, A+B= cyclopentanene,

substituted with an amino group with R5= methyl and R6= hydrogen.

Gilligan et. al. teaches compounds of the formula in claim 1, pyrazolo[1,5-a]pyrimidines, where R1= methyl, R3= methyl, R4= 2,4-dichlorophenyl, R2= hydrogen, A+B= unsubstituted cyclcopentyl. See columns 75-76, example 23.

Gilligan et. al. differs from the instant claims in the substitution of B, an unsubstituted cyclopentyl versus Applicants' aminomethyl. The reference teaches that A+B can be substituted with many substituents, including methylamino according to the genus of formula (1) in column 8 of the reference. See also column 8, lines 50; and column 9, lines 9, 20 and 50-53. This is one of the many compounds which renders said compounds obvious.

The same argument used for the above 103 rejection applies here too.

Thus, said claims are rendered obvious by Arvanitis et. al.

The following Applications all have similar situations:

U.S. 6191131

U.S. 6313124

U.S. 6124289

U.S. 6136809

U.S. 7094782

Double Patenting

The terminal disclaimer for U.S. Patent 6372743 and 6476038 has been received and approved.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susanna Moore whose telephone number is (571) 272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Susanna Moore/
Examiner, Art Unit 1624

/Brenda L. Coleman/
Primary Examiner, Art Unit 1624